Promoting Safety in Clinical Research at the University of Pennsylvania

The University of Pennsylvania is committed to ensuring that its clinical research programs meet the highest possible standards for patient safety. On its own initiative, the University has worked to develop an internal process and policies to promote compliance with all of the regulations that govern this critical area.

The University=s desire to achieve the highest quality of research protection led it to commission, in May of 1999, an external review of its Institutional Review Boards (IRB). By February 2000, the University had mandated strict adherence to regulatory requirements governing continuing reviews and adverse event reports, educated IRB members and staff about expedited review requirements, and established a new database to track reviewers and monitor IRB discussion and recommendations for changes in protocols and consent forms. Subsequently, the University created a free-standing Department of Medical Ethics, which works to further promote an informed dialogue about research issues. The University also implemented communication tools such as a new website and a new brochure intended to disseminate IRB information to the University community.

At the forefront of the University=s effort to promote compliance in the human research arena was the establishment in March 2000 of a University-wide oversight committee to coordinate all aspects of human research subject protections, and the September 2001 creation of the Office of Human Research (OHR), a School of Medicine-based Center working under the auspices of the Vice Dean for Research and Research Training. The OHR=s mission is to promote human research for the advancement of healthcare while ensuring the highest level of research participant safety and facilitating the highest quality research. Today, advanced through OHR and efforts such as those discussed above, the fundamental aspects of Penn=s compliance model, which the University has voluntarily created and implemented, include:

1. The training, education and certification of all clinical investigators, as a prerequisite to the conduct of research;

2. An internal system of monitoring clinical research at the University, overseen by OHR;

3. A strengthened and revitalized Institutional Review Board, armed with the technological and financial resources to fulfill its mission;

4. Specific, written policies which provide sanctions for investigators who fail to comply with the regulations in this arena; and

5. A newly implemented Conflict of Interest Policy targeted specifically at the conduct of clinical trials.

Training and Education of Clinical Investigators

Penn has developed a Mandatory Patient Oriented Research Training curriculum for all investigators who participate in clinical research, and their clinical research coordinators. There are currently two levels of certification. A patient-oriented research basic training course, required of all investigators conducting human research and their clinical research coordinators, consists of the following topics:

1. Historical Perspectives on Human Subject Protection
2. IRB and Federal Regulations
3. Conflict of Interest

In addition, a second, advanced-level course in Good Clinical Practices training is required for all investigators and clinical research coordinators conducting clinical trials. This course includes:

1. Introduction to Good Clinical Practices (GCP)
2. FDA Regulations for Clinical Research (IND/IDE)
3. Informed Consent
4. Adverse Events
5. Data and Safety Monitoring
6. FDA Audits

Upon successful completion of the web-based program, which employs sophisticated, interactive features, researchers receive a certification of completion. The IRB will not review a protocol application from the School of Medicine, or one which involves federal funding, absent such certification.

A second significant aspect of the education of clinical researchers has been the development of strengthened Standard Operating Procedures (SOPs). These SOPs, which have been prepared to address the roles and responsibilities of sponsor/investigators as well as investigators, provide detailed guidance and policies for conducting GCP-compliant research at the University.

Monitoring and Oversight of Clinical Research

The University understands that no compliance structure is complete without a program to monitor the clinical research.

The first step in the University=s monitoring, which has been completed, was an external, regulatory review of 26 faculty who serve as sponsor/investigators and were responsible for a total of 101 research protocols. This regulatory review was conducted by an independent contract research organization. The findings were communicated to

both the central University Oversight Committee and a School of Medicine Advisory Committee. OHR reviewed the findings with each individual investigator, documented the necessary responses to them, and tracked completion of these responses.

The second phase, consisting of internal monitoring of clinical research, is on-going. The IRB, beginning in 2000, implemented a formal process of risk assessment of clinical research. This process is used by the IRB to determine those studies requiring oversight by groups independent of the principal investigator. The IRB has currently identified and designated a total of 125 studies, conducted by 74 principal investigators, as satisfying the criteria for a high risk study, and these are the first set of studies to be reviewed. OHR has begun to monitor all of these investigators, verifying that they are complying with all applicable regulatory standards. Particular emphasis in this monitoring effort has been placed upon informed consent, adverse event reporting and communications with FDA and the IRBs. OHR will continue with this initiative as part of its core program of quality assurance and improvement.

In general, OHR works to provide assistance in the areas of IND decision-making and submission, development of site monitoring plans, preparation of study documents, and the assessment and organization of study portfolios. With respect to research compliance, OHR provides ongoing guidance in areas such as the validation of local monitoring plans, the preparation of GMP and GLP documentation, and the development of QA corrective action plans. OHR is also involved in all facets of the management of complaints from subject volunteers, researchers or sponsors regarding clinical research at Penn, including the intake of direct calls and referrals, assessment of each call and follow-up with involved parties, documentation of findings, and the development, implementation and oversight of management plans.

The Revitalized Penn IRBs

The University of Pennsylvania recognizes that its Institutional Review Boards are the very foundation upon which a successful system of oversight of clinical research must be based. Dramatic progress has been made in strengthening the IRB structure at Penn. Between FY >98 and FY >05, the resources of the Office of Regulatory Affairs (ORA), which is responsible for staffing the IRBs, have been increased nearly five-fold, from five full-time employees to 23 full-time employees.

Each IRB member and the ORA staff receive education and training appropriate to their function. In November 2004, the University licensed a web-based presentation tool to facilitate this education and implemented web-based trainings for both IRB members and IRB administrators. The University is also preparing an extensive IRB manual in collaboration with an outside consultant, and is working to develop social-behavioral faculty and student training modules with the help of a faculty advisory group.

IRB members and ORA staff are also guided by detailed IRB SOPs, formally approved in October 2001 and revised annually, which provide the specific rules and

responsibilities governing the IRB=s operation. Originally written to cross-link with sponsor-investigator SOPs, Investigator SOPs, and federal regulations and guidance documents, there are approximately 35 approved SOPs that clearly delineate the requirements in several IRB-related areas, including general IRB administration, IRB organization, functions and operations of IRBs, review of research, reviews requiring special administration, IRB communication and notification, informed consent, investigator responsibility and quality assurance.

Specific SOPs set forth the function and responsibilities of the Executive Chair and Chairs of the IRB. Reporting directly to the Vice Provost for Research, the Executive Chair of the IRB assists the Director and Associate Director of the ORA in policy development and serves as the chief medical liaison with the Director and Director=s staff. The Executive Chair also reviews and approves most expedited actions following review and referral by staff, serves as a quality reference across IRBs, and assists in IRB member recruitment. The Chairs of the IRB are responsible for controlling the flow of IRB meetings and serve as the primary coordinator contact for the clarification of IRB minutes and letters. The Chairs also assist coordinators and staff in assigning reviewers, and review and approve expedited actions for protocols as necessary or as determined by the Board.

ORA=s system has also developed technological advances to further regulatory compliance and the precise tracking of adverse events. The Adverse Event Reporting System provides a central database to facilitate the monitoring, auditing, and both expedited and annual reporting of serious adverse events to the IRB, OHR and other internal compliance offices at the University. This database, which allows for easy access to historical and current data via any web browser, gives users the ability to create Voluntary Notice to Sponsor reports as well as immediate date/time stamped electronic reports to ORA. A second database tracking system identifies primary and secondary reviewers and monitors IRB discussion of substantive issues and recommendations for changes in protocols and consent forms, as reflected in the official minutes of the IRB. A 24-hour adverse event hotline, established in 2000, continues to function on nights and weekends, and is manned by the IRB Director and/or Associate Director.

In the Spring of 2003, the University commissioned an internal and external review of IRB operations and support, placing a specific emphasis on the assessment of IRB staff training/education and IRB member and office support. The reviewers recommended a further reorganization of the IRB in FY= 2004, including recruitment of a senior IRB administrator as Associate Director and the upgrading of the entire administrative staff. This upgrade facilitated the recruitment of three new Senior IRB Administrators. The reviewers also recommended enhancing the level of support for the Executive Chair and IRB Chairs, instituting an additional IRB to serve general medical protocols, providing an honorarium for community members, and developing enhanced training support for IRB staff, members and faculty in non-medical areas.

The University, in an effort to maintain and build upon this record of progress, has voluntarily decided to seek accreditation from the Association for the Accreditation of Human Research Protections Programs (AAHRPP). The University is actively preparing its accreditation application and plan for a formal submission in early 2005. The University anticipates an in depth, on-site evaluation of its IRB=s operations by AAHRPP in Summer 2005.

Coordination and Collaboration Between ORA and OHR

To ensure a maximum benefit is gained from the efforts being undertaken by the University to streamline its oversight of human research, great emphasis has been placed on the coordination and collaboration between the ORA and OHR. Representatives from ORA and OHR participate in twice monthly interface meetings. The two offices also collaborate on policy and template development efforts, as well as AAHRPP certification preparation. Currently, both the Director and the Associate Director of ORA and the Executive Chair of the IRB sit on the OHR Faculty Advisory Committee. Multiple OHR members sit on IRB committees, as appropriate.

Sanctions for Non-Compliance

The University has developed procedures to address investigators who fail to adhere to the regulatory standards governing clinical research at the University. These policies, entitled Management of Serious or Significant Regulatory Non-Compliance in Clinical Research, are delineated in the Office of Human Research=s written guidelines. They mandate that the School=s leadership, in conjunction with the University, swiftly address any such findings in order to promote the safety of those who volunteer to participate in clinical research. OHR, in conjunction with a committee of senior faculty, the Dean and the IRB, are collectively empowered to take a variety of measures, up to and including the suspension of a clinical trial and/or the complete suspension of a faculty member=s research privileges. Pursuant to the same policies, a series of detailed, remedial and corrective actions are implemented, and closely monitored, prior to the removal of such a suspension. Of course, all such suspensions are reported to the sponsor, FDA, OHRP, and funding agencies as appropriate, by the OHR and/or ORA.

These policies underscore the University=s strong commitment to compliance in clinical research. Having devoted significant resources to facilitate the achievement of the highest possible standards by its clinical investigators, the University has not, and will not, hesitate to sanction those who willfully fail to meet those standards.

Conflict of Interest Guidelines for Faculty Participating in Clinical Trials

The University recognizes it is particularly important that clinical research be insulated from potential conflicts of interest that might be perceived to influence its conduct or outcome. Therefore, for investigators involved in clinical trials, the

University implemented an additional set of requirements involving disclosure and prohibition of financial interests, which supplemented its standard conflict of interest policies. These guidelines are consistent with provisions of the AAMC white paper issued in December 2001, entitled AProtecting Subjects, Preserving Trust, Promoting ProgressCPolicy and Guidelines for the Oversight of Financial Interests in Human Subjects Research.@

The University=s policy presumes that researchers who have significant financial interest that constitute potential conflicts of interest may not participate in clinical trials. This presumption may be overcome only by a showing of compelling circumstances to the Conflict of Interest Standing Committee, and only upon the satisfaction of numerous safeguards, including adoption of an appropriate management plan. Any such plan must include full disclosure to subjects participating in the trial through the informed consent document, to the IRB and to research staff. In addition disclosure must be made in all presentations and publications of the data emanating from the trial. Review of faculty compliance with these conflict of interest management plans is part of the OHR compliance oversight functioning. Deliberate violation of these policies results in sanctions.